C9orf72 in myeloid cells suppresses STING-induced inflammation.

Journal: Nature

Publication Year: 2020

Authors: Madelyn E McCauley, Jacqueline Gire O'Rourke, Alberto Yanez, Janet L Markman, Ritchie Ho, Xinchen Wang, Shuang Chen, Deepti Lall, Mengyao Jin, A K M G Muhammad, Shaughn Bell, Jesse Landeros, Viviana Valencia, Matthew Harms, Moshe Arditi, Caroline Jefferies, Robert H Baloh

PubMed link: 32814898

Funding Grants: CIRM Stem Cell Biotechnology Training Program

Public Summary:
Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are neurodegenerative disorders that overlap in their clinical presentation, pathology and genetic origin. Autoimmune disorders are also overrepresented in both ALS and FTD, but this remains an unexplained epidemiologic observation(1-3). Expansions of a hexanucleotide repeat (GGGGCC) in the C9orf72 gene are the most common cause of familial ALS and FTD (C9-ALS/FTD), and lead to both repeat-containing RNA and dipeptide accumulation, coupled with decreased C9orf72 protein expression in brain and peripheral blood cells(4-6). Here we show in mice that loss of C9orf72 from myeloid cells alone is sufficient to recapitulate the age-dependent lymphoid hypertrophy and autoinflammation seen in animals with a complete knockout of C9orf72. Dendritic cells isolated from C9orf72(-/-) mice show marked early activation of the type I interferon response, and C9orf72(-/-) myeloid cells are selectively hyperresponsive to activators of the stimulator of interferon genes (STING) protein-a key regulator of the innate immune response to cytosolic DNA. Degradation of STING through the autolysosomal pathway is diminished in C9orf72(-/-) myeloid cells, and blocking STING suppresses hyperactive type I interferon responses in C9orf72(-/-) immune cells as well as splenomegaly and inflammation in C9orf72(-/-) mice. Moreover, mice lacking one or both copies of C9orf72 are more susceptible to experimental autoimmune encephalitis, mirroring the susceptibility to autoimmune diseases seen in people with C9-ALS/FTD. Finally, blood-derived macrophages, whole blood and brain tissue from patients with C9-ALS/FTD all show an elevated type I interferon signature compared with samples from people with sporadic ALS/FTD; this increased interferon response can be suppressed with a STING inhibitor. Collectively, our results suggest that patients with C9-ALS/FTD have an altered immunophenotype because their reduced levels of C9orf72 cannot suppress the inflammation mediated by the induction of type I interferons by STING.

Scientific Abstract:
Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are neurodegenerative disorders that overlap in their clinical presentation, pathology and genetic origin. Autoimmune disorders are also overrepresented in both ALS and FTD, but this remains an unexplained epidemiologic observation(1-3). Expansions of a hexanucleotide repeat (GGGGCC) in the C9orf72 gene are the most common cause of familial ALS and FTD (C9-ALS/FTD), and lead to both repeat-containing RNA and dipeptide accumulation, coupled with decreased C9orf72 protein expression in brain and peripheral blood cells(4-6). Here we show in mice that loss of C9orf72 from myeloid cells alone is sufficient to recapitulate the age-dependent lymphoid hypertrophy and autoinflammation seen in animals with a complete knockout of C9orf72. Dendritic cells isolated from C9orf72(-/-) mice show marked early activation of the type I interferon response, and C9orf72(-/-) myeloid cells are selectively hyperresponsive to activators of the stimulator of interferon genes (STING) protein-a key regulator of the innate immune response to cytosolic DNA. Degradation of STING through the autolysosomal pathway is diminished in C9orf72(-/-) myeloid cells, and blocking STING suppresses hyperactive type I interferon responses in C9orf72(-/-) immune cells as well as splenomegaly and inflammation in C9orf72(-/-) mice. Moreover, mice lacking one or both copies of C9orf72 are more susceptible to experimental autoimmune encephalitis, mirroring the susceptibility to autoimmune diseases seen in people with C9-ALS/FTD. Finally, blood-derived macrophages, whole blood and brain tissue from patients with C9-ALS/FTD all show an elevated type I interferon signature compared with samples from people with sporadic ALS/FTD; this increased interferon response can be suppressed with a STING inhibitor. Collectively, our results suggest that patients with C9-ALS/FTD have an altered immunophenotype because their reduced levels of C9orf72 cannot suppress the inflammation mediated by the induction of type I interferons by STING.